PATENT

Docket No. 24615/2014800

#16

4-25-03

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Marian Christopher

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In the application of:

Robert Patrick HOF *et al.*

Serial No.: 09/887,933

Filing Date: 22 June 2001

For: PROCESS FOR RACEMISING AN ENANTIOMER-ENRICHED SCHIFF BASE OF AN AMINO ACID AMIDE

Examiner: S. Kumar

Group Art Unit: 1621

BRIEF ON APPEAL

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

A Notice of Appeal was filed in this action on 9 December 2002, thus setting a date for filing of the Brief of 9 February 2003. A two month extension of time is filed herewith thus extending the time for response until 9 April 2003. This is an Appeal from the final rejection of claims 12-22, in the above-referenced application. In accordance with 37 C.F.R. § 1.192, this Brief, along with the Appendix, is filed **in triplicate** and is accompanied by the required fee.

1. Real Party in Interest

The real party in interest in this appeal is DSM N.V. by virtue of an assignment recorded in the U.S. Patent and Trademark Office on 22 June 2001, Reel/Frame: 011952/0327.

2. Related Appeals and Interferences

There are no other Appeals or Interferences known to the appellants, the appellants' legal representative, or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the present pending appeal.

3. Status of Claims

Claims 1-11 were contained in the original specification and were cancelled and replaced with claims 12-22 filed concurrently in a Preliminary Amendment. Pending claims 12-22 have been finally rejected. The claims involved in this appeal, claims 12-22, are presented in the Appendix attached hereto as Exhibit A.

4. Status of Amendments

Claims 12 and 22 were amended in the Amendment under 37 C.F.R. § 1.111, filed 19 April 2002, and Claim 12 was amended further in the Amendment under 37 C.F.R. § 1.116, filed 24 October 2002, which amendment has been entered according to the Advisory Action mailed 7 November 2002.

5. Summary of the Invention

The invention is directed to an improved process of more quickly and efficiently racemizing an enantiomer-enriched Schiff base of a primary amino acid amide in comparison to conventional processes, while substantially reducing the extent that byproducts are formed. Please see the present specification on page 1, lines 18-20. The process requires the use of a

strong base in an organic solvent, wherein the strong base is chemically reactive with water. The invention also requires the use of a Schiff base of a primary amino acid amide. A *primary* amino acid amide is an amino acid amide where the amide-NH_2 is unsubstituted, that is, there are 2 hydrogen atoms attached to the N. Please see the present specification on page 1, lines 21-22. In contrast, a skilled artisan would understand that in the case of *secondary* amino acid amides, one of the hydrogen atoms on the N is replaced with a non-hydrogen moiety.

6. Issue

Whether *prima facie* obviousness under 35 U.S.C. § 103 has been established for claims 12-22 based on U.S. Patent No. 5,674,857 issued to Hijiya *et al.* (Hijiya), where Hijiya does not provide motivation to substitute its secondary amino acid amides for the claimed primary amino acid amides, as there is no teaching or suggestion of a primary amino acid amide in Hijiya nor expectation that such substitution will be equivalent or successful.

7. Grouping of Claims

The claims stand or fall together.

8. Argument

Hijiya Does Not Render Obvious the Present Claims.

a) Hijiya Does Not Disclose All Claim Limitations

In order to establish a *prima facie* case of obviousness it is necessary that all of the claim limitations are found in the cited reference. Please see MPEP §2143.03. There is no teaching or suggestion in Hijiya of the racemization of a Schiff base of a *primary* amide of an amino acid. As can be seen in Hijiya's Schiff base of an amino acid amide, *i.e.*, formula (2) or (3), that is reacted with a base, none of the nitrogen atoms are linked to two hydrogen atoms as is required

by definition in a primary amino acid amide, but rather are linked to only one hydrogen atom and thus are by definition secondary amino acid amides. The statement of the rejection in the final Office action appears to acknowledge this fact (see page 3, third paragraph, of the final Office action mailed July 9, 2002).

Although such lack of teaching or suggestion is sufficient to establish that a *prima facie* case of obviousness has not been established, there are additional reasons as outlined below as to why a *prima facie* case has not been established.

b) Hijiya Does Not Teach Selection of Primary Amide for Which a Successful Racemization Process is Expected

Other elements needed to establish *prima facie* obviousness are that there must be a suggestion or motivation to modify the reference to arrive at the claimed invention and that there must be a reasonable expectation that such a modification would be successful. Please see MPEP § 2143. Hijiya does not teach or suggest the racemization of Schiff bases of primary amides in general and provides no suggestion or motivation to modify the secondary amino acid amides disclosed therein to arrive at the primary amino acid amides used in the claimed invention. Even if for the sake of argument Hijiya teaches a genus of amino acid amides, there is no indication that selection of one species of such a genus of amides, namely a primary amino acid amide, would reasonably be expected to be successful. Nowhere in Hijiya is it suggested that reacting a base as claimed with a Schiff base of a primary amino acid amide would result in a faster racemization process in comparison to conventional processes. Please see the present specification, for example, page 1, lines 9-31. Rather, Hijiya's stated objective is to use low cost starting materials to make one subset of secondary amino acid amides, namely D-amino acid-N-(S)-α-alkylbenzylamides. Please see Hijiya, column 1, line 58 and column 3, lines 39-43. As

such, the two remaining elements necessary for establishing *prima facie* obviousness have not been shown.

c) Hijiya Does Not Suggest that a Primary Amide Would Function Equivalently as a Secondary Amide Nor is Hijiya's Process Directed to the Same Problem as the Claimed Invention

Additionally, it is respectfully submitted that there is no indication of why a skilled artisan would expect that a *primary* amide of an amino acid would function equivalently in the teachings of Hijiya. Hijiya's secondary amide of an amino acid has two chiral centers (one at the amino acid's alpha carbon, which is labeled with an asterisk in any of figures (1), (2) or (3), and the second at the carbon to which R_2 is attached) which permits the formation of two diastereomers. A skilled artisan would understand that a compound that contains two chiral centers form two diastereomers which have different chemical and physical properties. Such different properties result because the diastereomers are not mirror images of each other. Please see Stanley H. Pine *et al.*, *Organic Chemistry*, 120 (1980), attached. This phenomenon is illustrated by the fact that Hijiya's "D" diastereomer crystallizes out of the liquid that contains the "L" diastereomer. Please see column 1, lines 66-67 of Hijiya. Such crystallization facilitates the conversion and isolation of the "D" stereoisomer and, upon hydrolization thereof, is converted to the "D" version of the starting material that has the opposite chirality of the "L" starting material. Such isolation is in contrast to racemization *per se,* which is defined in the specification as lowering the enantiomeric excess of enantiomer-enriched compounds. See Hijiya column 2, lines 6-33, and the present specification on page 2, lines 4-5. For example, if the enantiomeric excess is lowered to 0, then a racemate is present (*i.e.,* equal amounts of each mirror image enantiomer). As such, the present invention does not rely on the phenomenon described in Hijiya and is directed to a different problem in the art.

Moreover, the above teachings of Hijiya *cannot* be performed by preparation of a primary amide in place of the secondary amide because the resulting primary amide of an amino acid would only have a single chiral center at the alpha carbon. Racemization at that center would create two enantiomers that cannot be separated by the method disclosed in Hijiya. Pine, *supra*, at 117-118. Therefore, Applicants respectfully submit that there is *no* expectation of success in the asserted modification of Hijiya to utilize a primary amide (see the basis of the requirement at MPEP 2143.02 and the cases cited therein). To the contrary, there is evidence that the teachings of Hijiya would lead the artisan of ordinary skill *away from* the use of a primary amide and toward the use of a secondary or tertiary amide because only secondary or tertiary amides can introduce a second chiral center into the resulting amide.

c) Hijiya Does Not Point to Particular Bases that are Required in Claimed Invention

It is respectfully submitted that there must be more than mere disclosure of a species (*i.e.*, a base reactive with water) to provide the motivation to combine such disclosure with another species (*i.e.*, primary amino acid amide, albeit not disclosed in Hijiya) even where the reference discloses the genus. *In re Baird*, 16 F.3d 380, 29 US.P.Q.2d (BNA) 1550 (Fed. Cir. 1994); *In re Jones*, 958 F.2d 347, 21 US.P.Q.2d (BNA) 1941, 1944 (Fed. Cir. 1992). There is no recognition in Hijiya of the necessity to use the species of a base reactive with water. Any of the bases disclosed in column 4, lines 1-6 of Hijiya may be used in the process, and thus a skilled person would not be lead to only those bases that are reactive with water. Thus, there is insufficient motivation to select the particular species of base used in the claimed invention.

d) Motivation Provided in Advisory Action is Insufficient

The asserted motivation set forth in the Advisory Action is misplaced, namely "Inasmuch as there is [a] chiral center, there is motivation to use the process of Hijiya et al for primary

amide racemization." As discussed above, more than simply the presence of chiral center is needed to arrive at the claimed method, that is, motivation to select a primary amides and motivation to select the type of base expected to be successful is needed. Regardless of motivation, all of the claim limitations must be present as well as an expectation of success. As such, not a single element necessary for establishing *prima facie* obviousness has been appropriately established.

9. Appendix

An Appendix containing a copy of the claims as currently pending is attached.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Brief, or to credit any overpayment, to Deposit Account No. 03-1952.

Respectfully submitted,

Dated: April 9, 2003 By: _____

Carolyn A. Favorito
Registration No. 39,183

Morrison & Foerster LLP
3811 Valley Centre Drive
Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5195
Facsimile: (858) 720-5125

APPENDIX

12. A process for racemising an enantiomer-enriched Schiff base of a primary amide of an amino acid which process comprises contacting said enantiomer-enriched Schiff base of a primary amide of an amino acid with a strong base in an organic solvent,

wherein said strong base is chemically reactive with water.

13. The process of claim 12 wherein the strong base is a metal alkoxide, a metal alkyl, a metal amide, or a metal hydride.

14. The process of claim 13 wherein the strong base is a metal alkoxide.

15. The process of claim 12 wherein the strong base is present in an amount of 0.001-1000 mole% relative to the enantiomer-enriched Schiff base.

16. The process of claim 15 wherein the strong base is present in an amount of 0.1-100 mole% relative to the enantiomer-enriched Schiff base.

17. The process of claim 12 wherein the enantiomer-enriched Schiff base is an N-benzylidene primary amino acid amide.

18. The process of claim 12 wherein the enantiomer-enriched Schiff base is derived from an aliphatic primary amino acid amide.

19. The process of claim 18 wherein the enantiomer-enriched Schiff base is derived from tertiary-leucine amide.

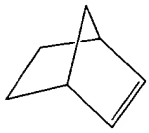
20. The process of claim 12 wherein the organic solvent is an aromatic hydrocarbon, a cyclic aliphatic hydrocarbon or an ether.

21. The process of claim 20 wherein the organic solvent is an aromatic hydrocarbon.

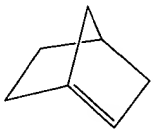
22. The process of claim 12 wherein said enantiomer-enriched Schiff base has been prepared from the primary amide of the amino acid in said organic solvent.

PROBLEM 4-25 | **Draw a conformational structure for cyclohexene.**

Many small bicyclic molecules can possess double bonds as long as the multiple bond is not located at a bridgehead carbon atom. Norbornene is a well-known compound, but the isomer with a bridgehead double bond is, at this time, unknown.

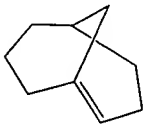


Norbornene
(Bicyclo[2.2.1]-2-heptene)

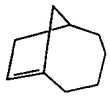


Bicyclo[2.2.1]-1-heptene
Unknown compound

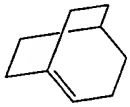
Bredt's rule states that small bicyclic compounds with the double bond at a bridgehead should be highly strained. Attempts to push Bredt's rule to the limit have resulted in the preparation of the following bridgehead alkenes:



Bicyclo[3.3.1]-1-nonene



Bicyclo[4.2.1]-6-nonene



Bicyclo[3.2.2]-1-nonene

PROBLEM 4-26 | **Discuss the spatial orientation of the four single bonds connected to the double bond in each of the above bridgehead bicycloalkenes.**

Many explanations are employed to rationalize the formation of strained molecules. We encountered the concept of a bent bond as an explanation for bonding in cyclopropane (sec. 4-3*D*). Changes in hybridization provide another explanation. Acceptable bond angles can be larger if they possess more *s* character or smaller if they have more *p* character (sec. 3-4*A*). It has been suggested that the orbitals of the carbon-carbon bonds of cyclopropane have only about 17 percent *s* character and represent approximately sp^5 hybridization.

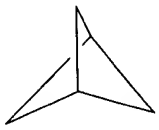
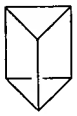
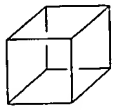
A series of fascinating compounds which duplicate interesting geometrical figures have been prepared in recent years. Structures and IUPAC names of some of these strained compounds are compiled in table 4-3.

4-4 CHIRALITY AND OPTICAL ACTIVITY

Probably the most fascinating, and often subtle, type of stereoisomerism is that which can give rise to optical activity. When Biot, in 1815, reported that certain naturally occurring organic materials possess the ability to rotate the plane of polarized light, he initiated a great deal of interest and associated experimentation among his scientific colleagues. Over the next 60 years many scientists made important contributions to the evidence for the occurrence of optical activity, but

TABLE 4-3

Some strained polycyclic compounds.

Structure	IUPAC Name	Common Name
	Bicyclo[1.1.0]butane	Bicyclobutane
	Bicyclo[1.1.1]pentane	A propellane
	Tetracyclo[2.2.0.$0^{2,6}$.$0^{3,5}$]hexane*	Prismane
	Pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane*	Cubane

*The nomenclature of polycyclic compounds follows the pattern used for bicyclic structures. An additional requirement is that the numbers of the carbon atoms to which the fourth or additional carbon chain is connected are indicated as superscripts to the chain designation.

none grasped the relation between the data and molecular structure. In 1874 van't Hoff and Le Bel independently provided the theory which not only interpreted the phenomenon of optical activity but also showed how a three-dimensional model of molecules could account for much of the confusion relative to structure.

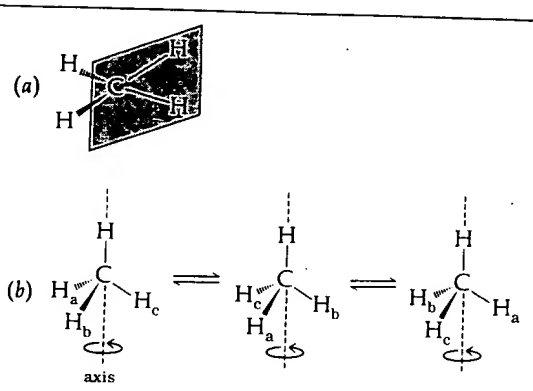
A. Symmetry properties of organic molecules

We have considered the structure of methane many times during our discussions of molecular structure. It should be obvious that methane is a molecule with high symmetry. It possesses, for example, *planes of symmetry* passing through the carbon and any two of the hydrogen atoms (fig. 4-22*a*) as well as a threefold *axes of symmetry* along each C—H bond (fig. 4-22*b*). A plane of symmetry divides a molecule into two halves which are mirror images of each other. An axis of symmetry is defined as a line which passes through the molecule so that a rotation of $360°/n$ about this axis leads to a three-dimensional structure which is indistinguishable from the original. All molecules possess a onefold axis of symmetry ($n = 1$) since rotation of 360° about any axis leads to the identical structure.

If we look at the substituted methanes chloromethane (CH_3Cl), dichloromethane (CH_2Cl_2), and trichloromethane ($CHCl_3$), we again see that each has at least

FIGURE 4-22

Symmetry elements for methane: (a) one plane of symmetry; (b) one threefold axis of symmetry.



one plane of symmetry. The presence of at least two identical atoms on the central carbon provides that element of symmetry.

PROBLEM 4-27 | **Draw one plane of symmetry for each of the following molecules: CH_3Cl, CH_2Cl_2, and $CHCl_3$. Do these compounds have any axes of symmetry?**

Now consider the compound 2-butanol. Four different groups are attached to the number two carbon atom. We can find no planes or other elements of symmetry associated with the atom. *The number two atom of 2-butanol is asymmetric.*

Another way to recognize that asymmetry is to compare three-dimensional formulas of 2-butanol. We find that the compound can be represented by two nonsuperimposable mirror image structures (fig. 4-23). Stereoisomers that are related to each other as *nonsuperimposable mirror images* are known as *enantiomers.*

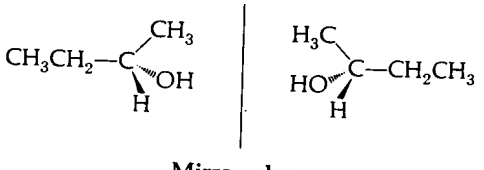
PROBLEM 4-28 | **Use molecular models and three-dimensional drawings to show that**

a The enantiomers of 2-butanol are not superimposable.

b The mirror images of CH_3Cl, CH_2Cl_2, and $CHCl_3$ are each identical to the original molecules.

FIGURE 4-23

Enantiomers of 2-butanol.



Mirror plane

Enantiomers are related to each other in the same way that a right hand is related to a left hand. Molecules that are related to each other in that way are said to be *chiral*. The number two carbon atom of 2-butanol is the *chiral atom*, or the *chiral center*, of the molecule. One of the easiest ways (though not the only way) to recognize chirality is to look for carbon atoms connected to *four different* groups.

B. Optical activity

When Biot observed the rotation of polarized light by certain organic compounds, he was utilizing the method by which we still differentiate enantiomers in the laboratory. A solution of the compound under consideration is placed in an instrument known as a *polarimeter*. The direction of rotation of the plane of polarized light is observed as the light passes through the sample. If the light is rotated in a *clockwise* direction, the sample is said to be *dextrorotatory* and is designated as (+) or *d*. When a sample rotates the plane of polarized light in a *counterclockwise* direction, it is said to be *levorotatory* and is designated as (−) or *l*. *Enantiomers rotate the plane of polarized light in opposite directions but with equal magnitudes.*

Although chirality is a necessary prerequisite for optical activity, chiral compounds are not necessarily optically active. In the laboratory a chiral compound such as 2-butanol will normally be found as an equal mixture of the two enantiomers. Since the two enantiomers rotate the plane of polarized light in equal but opposite directions, no net optical rotation is observed. A chiral compound which is optically inactive because it is composed of an equal mixture of enantiomers is said to be *racemic* and is designated as (±) or *dl*.

PROBLEM 4-29

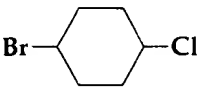
Which of the following compounds are chiral and thus capable of existing in optically active forms? Identify the chiral center or centers.

a $CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CH_3$

b $CH_2{=}CH\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3$

c 1-Chlorobutane

d 3-Chloro-2-butanol

e 

f 4-Bromo-1-chlorocyclohexene

g $C_6H_5\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$

h 1,3-Dimethylbenzene

C. Absolute configuration

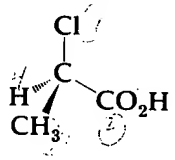
Enantiomers have a curious relation in comparison with other isomers we have encountered. They are nonsuperimposable, yet their structures appear to be identical. Distances between atoms surrounding the chiral center of one enantiomer are the same as those in its mirror image enantiomer. Experiments have clearly demonstrated that most of the physical properties of enantiomers (melting

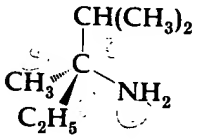
point, boiling point, solubility) are identical, and under most laboratory circumstances the enantiomers show identical chemical reactivity. What, then, is different about enantiomers?

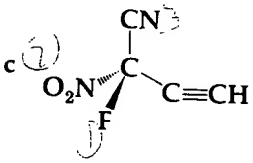
The difference is the *spatial sequence* of the atoms or groups connected to the chiral atom, i.e., the *configuration*. Molecules related to each other as nonsuperimposable mirror images (enantiomers) have *opposite* configurations. The *absolute configuration* describes the arrangement in space of the four groups attached to the chiral center.

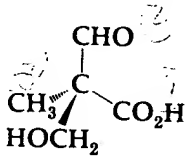
A general system for designating absolute configuration is based upon the Cahn-Ingold-Prelog priority system (sec. 4-1*B*). Each group attached to the chiral carbon atom is assigned a number 1, 2, 3, or 4; 1 is the highest-priority group, and 4 is the lowest. For example, the groups attached to the chiral center of 2-butanol are assigned 1 = OH, 2 = CH_2CH_3, 3 = CH_3, and 4 = H. The molecule is then viewed from the *side opposite* the group of lowest priority (4 = H). The order of decreasing priority (1, 2, 3) of the remaining groups represents either a clockwise or a counterclockwise sequence. If the sequence is *clockwise*, the molecule is assigned the (*R*) (*rectus*, "right") configuration. A *counterclockwise* sequence represents an (*S*) (*sinister*, "left") configuration (fig. 4-24).

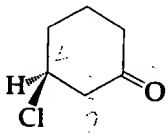
PROBLEM 4-30 **Assign an (*R*) or (*S*) absolute configuration to each of the following molecules:**

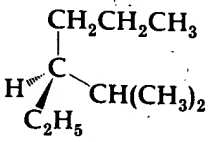
a 

b 

c 

d 

e 

f 

PROBLEM 4-31 **Draw a three-dimensional structural formula for each of the following compounds:**

a (*R*)-2-Hydroxypropanoic acid

b (*R*)-2,3-Dibromopropanal

c (*S*)-3-Methyl-3-methoxy-4-hexen-2-one

d (*R*)-3-Cyanocyclopentanone

e (*S*)-3-Ethylhept-1-en-5-yne

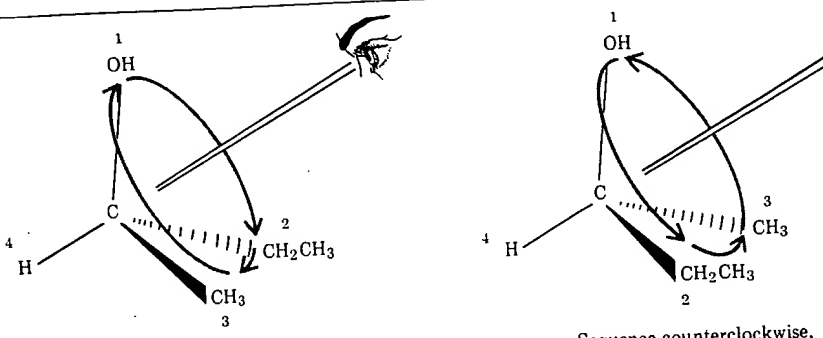
f (*R*)-2-Deuteriopropanoic acid

D. Relative configuration

Unfortunately, it is not easy to determine the absolute configuration of a chiral compound. The most obvious experimental technique, measurement of optical

FIGURE 4-24

Absolute configuration designations for the enantiomers of 2-butanol.



rotation, physically characterizes the compound but provides no simple indication of configuration. Many enantiomers change their signs of rotation as the wavelength of light is varied and some even have different signs in different solvents.

Relative configurations around the chiral centers of many compounds have been established. One optically active compound is converted to another by a sequence of chemical reactions which are *stereospecific;* that is, each reaction is known to proceed spatially in a specific way. The configuration of one chiral compound can then be related to the configuration of the next in the sequence. To establish absolute configuration, a chemist need only carry out sufficient stereospecific reactions to relate a new compound to another of known absolute configuration.

Historically, the configuration of *d*-(+)-glyceraldehyde (*d*-(+)-2,3-dihydroxypropanal) served as the standard to which all configuration was compared. Toward the end of the nineteenth century Emil Fischer arbitrarily assigned the absolute configurations depicted in fig. 4-25 to the enantiomers of glyceraldehyde. At that time there was no clear basis for the choice.

In 1951 an X-ray crystallographic technique was employed to determine the absolute configuration of the sodium rubidium salt of tartaric acid. Since (+)-tartaric acid had previously been related to the configuration of (+)-glyceraldehyde, the *absolute configurations* of glyceraldehyde enantiomers *were established.* Luckily (a 50-50 chance), the earlier assignments by Fischer proved to be correct, and now all configurations relative to glyceraldehyde are absolute.

FIGURE 4-25

The absolute configurations of glyceraldehyde enantiomers.

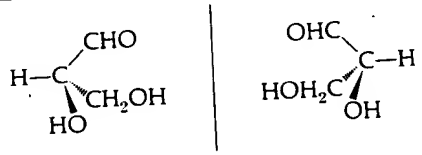
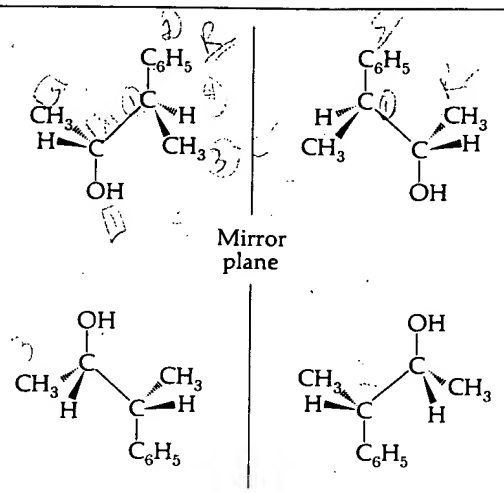


FIGURE 4-26

Stereoisomers of 3-phenyl-2-butanol.



E. Several chiral centers

The number of stereoisomers increases rapidly with an increase in number of chiral centers in a molecule. We can calculate the maximum number of possible stereoisomers from the formula stereoisomers $= 2^n$, where n = number of chiral centers.

Consider 3-phenyl-2-butanol, a compound possessing two chiral atoms. Four isomers can be represented by three-dimensional drawings (fig. 4-26). We see that the four structures consist of two pairs of enantiomers. But what is the relation between one pair of enantiomers and the other? Drawings or molecular models illustrate that either enantiomer of one pair is not a mirror image of nor is it superimposable on either enantiomer of the other pair. Stereoisomers which are *not mirror images* are known as *diastereomers*. Whereas enantiomers are identical in all physical properties except their signs of optical rotation, diastereomers have different physical and chemical characteristics.

PROBLEM 4-32

a Assign (*R*) and (*S*) configurations to the chiral centers of all four stereoisomers of 3-phenyl-2-butanol.

b The molecules are relatively free to rotate about the central carbon-carbon bond. Will the conformation at any instant affect the configurational assignments?

PROBLEM 4-33

a Draw three-dimensional structural formulas for the stereoisomers of the important amino acid threonine (2-amino-3-hydroxybutanoic acid).

b Assign (*R*) and (*S*) configurations to the chiral centers of each molecule.

c Indicate which structures are enantiomers and which are diastereomers.

The difference in physical properties of diasteromers is the basis of the most common method for the separation of enantiomers, the technique of *enantiomer*

resolution (also called optical resolution). Since enantiomers have identical physical properties, they cannot be separated by a usual laboratory method such as distillation or crystallization. Conversion of enantiomers to diastereomers enables separation to be accomplished (sec. 8-4).

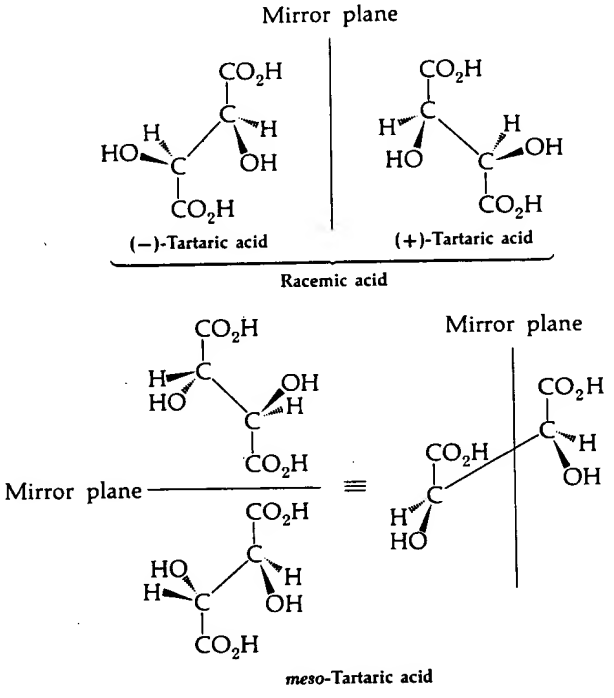
Pasteur carried out the first reported separation of enantiomers using a compound obtained during the preparation of wine. Tartaric acid (2,3-dihydroxybutanedioic acid), a compound with two chiral atoms, deposits as a potassium salt (tartar) during the fermentation of grape juice. Biot showed that the tartaric acid obtained from wine is usually dextrorotatory. Racemic acid also is obtained from the fermentation process, but it possesses no optical activity. Yet racemic acid has the same chemical composition as tartaric acid.

Pasteur observed that crystals of the sodium-ammonium salt of racemic acid exist in two different shapes: one structure right-handed and the other left-handed. He separated the two crystal forms by hand and found that one rotated the plane of polarized light to the right (dextrorotatory) and the other rotated the light to the left (levorotatory). By mixing equal amounts of the optically active acids recovered from the separated salts, Pasteur demonstrated that racemic acid is a mixture of equal portions of dextrorotatory and levorotatory tartaric acid, i.e., a racemic mixture (fig. 4-27).

The Pasteur experiment proved to be extremely important in the early development of the structural theories of organic chemistry. Yet some degree of luck was involved. The material that Pasteur worked with is unusual in that it is the only known tartrate salt for which the two enantiomers deposit in different crystal forms. Furthermore, the different crystals are formed only below 25° and might

FIGURE 4-27

Stereoisomers of tartaric acid.



not have been observed if Pasteur had been working in a region where the climate is warm.

Racemic acid accounts for only two of the expected isomers of tartaric acid. We predict that a maximum of four stereoisomers ($2^2 = 4$) could exist, but only three isomers are actually found: the two optically active enantiomers which make up racemic acid and an optically inactive isomer.

Tartaric acid illustrates an important geometrical property of diastereomers: *molecules possessing two or more chiral centers are not necessarily chiral.* We see (fig. 4-27) that the two additional structural formulas drawn for tartaric acid are superimposable mirror images. They are, in fact, identical. Compounds that have chiral centers but are themselves achiral (nonchiral) are known as *meso compounds.* Meso compounds possess an element of symmetry. Recognition of a plane of symmetry is usually the easiest way to detect a meso compound.

Physical properties of the tartaric acid stereoisomers are compiled in table 4-4. The properties of the *d* and *l* isomers are identical (other than the sign of optical rotation) and are different from those of the meso form. We also find that the melting point of racemic acid is different from that of either the *d* or *l* isomers of which it is composed. Racemic mixtures usually have melting points higher than the melting point of either pure enantiomer. Intermolecular attractions between *d* and *l* enantiomers within the crystal lattice are generally stronger than those between either of the pure enantiomers.

TABLE 4-4

Physical properties of tartaric acids.

Compound	mp, °C	Specific Rotation at 25°C	Solubility in H_2O, g/100 ml
d-Tartaric acid	170	+11.98°	$147^{(25°)}$
l-Tartaric acid	170	−11.98°	$147^{(25°)}$
Racemic acid	206	0	$25^{(25°)}$
meso-Tartaric acid	140	0	$120^{(15°)}$

PROBLEM 4-34 **What is the relation between the absolute configurations of the chiral atoms in (+)- and in (−)-tartaric acid? In *meso*-tartaric acid?**

The same stereochemical principles apply to both cyclic and acyclic compounds. For example, the two chiral centers of cyclopropane-1,2-dicarboxylic acid lead to three stereoisomers: a pair of trans enantiomers and one cis form which is meso (fig. 4-28).

We also find that the trans isomer of 1,2-dimethylcyclohexane exists as a pair of enantiomers. The diequatorial conformer is markedly favored and equilibration does not alter the diastereomer relation (fig. 4-29*a*). In contrast, stereochemical relationships in the cis isomer are complicated by the superposition of conformational equilibration on configuration. Thus *cis*-1,2-dimethylcyclohexane is optically inactive and not resolvable at room temperature even though we are able to draw two enantiomeric structural formulas (fig. 4-29*b*). Configurations rapidly interconvert through conformational inversion so that the cis isomer is actually a meso compound.